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Newcastle University

Health Technology Briefing
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Giroctocogene fitelparvovec for haemophilia A

Company/Developer	Pfizer Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 16130	NICE ID: 9772	UKPS ID: 659457

Licensing and Market Availability Plans

Currently in phase II and III clinical development.

Summary

Giroctocogene fitelparvovec is in development for the treatment of moderately severe to severe haemophilia A in adult males. Haemophilia A is a rare bleeding disorder, caused by lack of blood clotting factor VIII which facilitates blood clotting and reduces bleeding events. The absence of factor VIII makes patients prone to excessive and uncontrolled bleeding. In severe cases, this can result in spontaneous bleeding into the joints, muscles or brain causing serious complications. The inability of their blood to clot means that patients are at high risk of internal bleeding, including from the brain, increasing their mortality risk. Haemophilia A is treated with replacement factor VIII (FVIII) to restore blood clotting and prevent bleeding. Most of the current treatments include frequent intravenous infusions with FVIII concentrate for disease prevention which can affect patient adherence. Therefore, there is a need to develop additional treatment options to increase adherence in these patients.

Giroctocogene fitelparvovec is a medicinal product administered intravenously. Giroctocogene fitelparvovec is a gene therapy that delivers a copy of the gene that encodes for factor VIII in a patient's liver cells. This medicinal product helps to maintain a sustained level of factor VIII in the blood of adult males with haemophilia A. If licensed, giroctocogene fitelparvovec will offer an additional treatment option for adult patients with moderately severe to severe haemophilia A.

Proposed Indication

For the treatment of adults with moderately severe to severe haemophilia A.[1]

Technology

Description

Giroctocogene fitelparvovec (SB-525; PF-07055480) is a gene therapy that contains a recombinant adeno-associated virus serotype 6 vector (AAV6) encoding the complementary deoxyribonucleic acid for B domain deleted human FVIII gene.[2] AAV–mediated gene transfer facilitates the delivery of a modified functional *F8* coding sequence to hepatocytes that subsequently synthesize FVIII at levels that may prevent bleeding events in the absence of exogenous FVIII.[3] The giroctocogene fitelparvovec expression cassette was designed for optimal liver-specific expression of FVIII protein and supports production of high yields of the transgene. The giroctocogene fitelparvovec transcriptional cassette incorporates multi-factorial modifications to the liver-specific promoter module, FVIII transgene, synthetic polyadenylation signal and vector backbone sequence.[2]

Giroctocogene fitelparvovec is currently in phase I/II (ALTA, NCT03061201) and phase III (AFFINE, NCT04370054) clinical development for the treatment of adult males with moderately severe to severe haemophilia A. In these trials, giroctocogene fitelparvovec is administered intravenously as a single infusion.[1,4]

Key Innovation

The need for frequent infusions with current therapies such as prophylaxis may be a barrier for compliance and adherence in patients with haemophilia A. Poor adherence has been significantly associated with an increased risk of breakthrough bleeding episodes and increased target joint bleeds in patients with haemophilia.[5] Adeno-associated virus (AAV) vectors are partially integrative vectors associated with a low risk of insertional mutagenesis and for their part exhibit the greatest potential for clinical use.[6]

In a preliminary phase I/II clinical trial, giroctocogene fitelparvovec has been shown to be well tolerated, without sustained adverse events and with minimal overall bleeding.[3] If licenced giroctocogene fitelparvovec will provide an additional treatment option for patients with haemophilia A.

Regulatory & Development Status

Giroctocogene fitelparvovec does not currently have Marketing Authorisation in the EU/UK for any indication.

Giroctocogene fitelparvovec is not currently in clinical development for any other indication.[7]

Giroctocogene fitelparvovec has the following regulatory designations/awards:[8,9]

- Orphan designation by the European Medicines Agency (EMA) in the EU in May 2020 for haemophilia A
- Orphan Drug designation by the U.S. Food and Drug Administration (FDA) in June 2020 for haemophilia A
- Fast Track designation by the FDA in June 2020 for severe haemophilia A
- Regenerative medicine advanced therapy (RMAT) designation by the FDA in June 2020 severe haemophilia A

Patient Group

Disease Area and Clinical Need

Haemophilia is a rare condition that affects the blood's ability to clot. It is usually inherited and most people who have it are male. Normally when people cut themselves, substances in the blood known as clotting factors combine with blood cells called platelets to make the blood sticky and stop the bleeding. People with haemophilia do not have as many clotting factors as there should be in the blood so they bleed for longer than usual.[10] Haemophilia A is a genetic bleeding disorder caused by insufficient levels of a blood protein known as factor VIII. Haemophilia A is caused by disruptions or mutation of the F8 gene located on the X chromosome. This mutation may be inherited or occur spontaneously, with no previous family history of the disorder.[11] The main symptom of haemophilia is prolonged bleeding. The symptoms of haemophilia A include a tendency to bruise easily; excessive bleeding from cuts; a tendency to bleed into joints and muscles (causing pain, swelling, and limitation of joint movement).[12] The symptoms of haemophilia can be mild to severe depending on the level of clotting factors a patient has. Individuals with mild haemophilia have factor VIII levels between 5% and 40% of normal; those with moderate haemophilia have levels between 1% and 5% of normal; and individuals with severe haemophilia have factor levels less than 1% of normal.[10,11] Haemophilia A is potentially life threatening as there is a risk of bleeding inside the skull (a brain or subarachnoid haemorrhage).[10]

Bleeding disorders are rare and complex, with haemophilia being the most widely recognised. Of the two main types of haemophilia, haemophilia A is the most common, with a prevalence of between 1:5000 and 1:10000 in males in England.[13] In the UK, 8,959 people are living with haemophilia A, of which 2,178 have severe haemophilia A.[14,15] In England, 2021-22, there were 2,729 finished consultant episodes (FCE) for hereditary factor VIII deficiency (ICD-10 code D66.X) resulting in 2,580 admissions (2,522 of which were male patients) and 3,165 FCE bed days.[16]

Recommended Treatment Options

There is currently no cure for haemophilia A. The condition requires on-demand treatment as an immediate response to bleeding episodes and regular injections of prophylaxis treatments to prevent bleeding episodes. Factor replacement therapy is the treatment of choice for people with haemophilia, which may be plasma-derived or recombinant.[17] Standard half-life (SHL) recombinant factor replacement factors are available which require intravenous infusions 2-3 times per week. Extended half-life (EHL) recombinant replacement factor are available which require less frequent administration (weekly); There are multiple EHL (and SHL) products approved by the EMA for the treatment and prevention of bleeding in patients with haemophilia A.[18,19]

Patients with prophylaxis of haemorrhage haemophilia A may be eligible for emicizumab (subcutaneous injection, every 1-4 weeks.[20]

Clinical Trial Information

Trial	NCT03061201; **ALTA;** A Phase 1/2, Open-Label, Adaptive, Dose-Ranging Study to Assess The Safety and Tolerability Of SB-525 (PF-07055480) (Recombinant AAV2/6 Human Factor 8 Gene Therapy) In Adult Subjects With Severe Hemophilia A **Phase II –** Active, not recruiting **Location(s):** US

	Estimated primary completion date: July 2024
Trial Design	Open label, sequential assignment
Population	N= 11 (actual); male subjects aged 18 years and older with severe haemophilia A (past evidence of circulating FVIII activity of < 1% normal); treated or exposed to FVIII concentrates or cryoprecipitate for at least 150 exposure days
Intervention(s)	Giroctocogene fitelparvovec administered as a single infusion
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Incidence of adverse events and serious adverse events [Time frame: Up to 5 years after giroctocogene fitelparvovec (SB-525; PF-07055480) infusion] • Changes in circulating FVIII activity [Time frame: Up to 5 years after giroctocogene fitelparvovec (SB-525; PF-07055480) infusion] See trial record for full list of outcome measures
Results (efficacy)	A single infusion of giroctocogene fitelparvovec gene therapy in patients with severe haemophilia A was generally well tolerated with associated increases in FVIII levels in the mild to normal range, without sustained AEs, and with minimal bleeding in the highest-dose cohort (3e13 vg/kg).[3,21]
Results (safety)	The most commonly reported treatment-related adverse events (AEs; n/N [%]), included elevated liver enzymes and infusion-related reactions: increased alanine aminotransferase, increased aspartate aminotransferase, pyrexia, and tachycardia. Treatment-related serious AEs were reported in 1 patient (in the 3e13-vg/kg cohort) who experienced hypotension and fever with onset ≈6 hours after giroctocogene fitelparvovec infusion; the events fully resolved with treatment and did not delay post-infusion discharge the next day.[3]

Trial	NCT04370054; 2019-004451-37; **AFFINE;** Phase 3, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of PF-07055480 (Recombinant AAV2/6 Human Factor VIII Gene Therapy) in Adult Male Participants With Moderately Severe to Severe Haemophilia A(FVIII:C≤1%) **Phase III –** Active, recruiting **Location (s):** 6 EU, UK, US, Canada and other countries **Estimated primary completion date:** March 2024
Trial Design	Open label, single group assignment
Population	N= 63 (estimated); male subjects with moderately severe to severe haemophilia A (Factor VIII activity < =1%); males who have been followed on routine Factor VIII prophylaxis therapy during the lead-in study (NCT03587116; C0371004) and have > = 150 documented exposure days to a Factor VIII protein product
Intervention(s)	Giroctocogene fitelparvovec administered as a single infusion intravenously
Comparator(s)	No comparator

Outcome(s)	Primary outcome: Annualized bleeding rate (ABR) [Time frame: 15 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of giroctocogene fitelparvovec is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Valoctocogene roxaparvovec for treating severe haemophilia A (GID-TA10682). Expected publication date to be confirmed.
- NICE technology appraisal in development. Concizumab for preventing bleeding episodes in haemophilia A or haemophilia B (GID-TA10972). Expected publication date to be confirmed.
- NICE technology appraisal in development. Efanesoctocog alfa for treating and preventing bleeding episodes in people of any age with previously treated haemophilia A (GID-TA11106). Expected publication date to be confirmed.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Emicizumab as prophylaxis in people with severe congenital haemophilia A without factor VIII inhibitors (all ages). August 2019.
- NHS England. Manual for Prescribed Specialised Services 2018/19. September 2018.
- NHS England. Clinical Commissioning Policy: Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages). 170067/P. July 2018.
- NHS England. Clinical Commissioning Policy: Immune Tolerance Induction (ITI) for haemophilia A (all ages). 16042/P. July 2016.
- NHS England. 2013/14 NHS Standard Contract for Haemophilia (all ages). B05/S/a.

Other Guidance

- British Society for Haematology. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. 2020.[22]
- World Federation of Haemophilia Guidelines for the Management of Haemophilia, 3rd edition. 2020.[17]
- British Society for Haematology. Diagnosis and Treatment of Factor VIII and IX Inhibitors in Congenital Haemophilia. 2013.[23]

Additional Information

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